REMARKS

This Amendment is supplemental to the Amendment filed on April 28, 2009 in response to the July 28, 2008 Office Action issued for this application. Pursuant to entry of the amendments submitted on April 28, 2009, claims 1, 3 and 18-31 are pending in the present application. Claims 1, 3, 21 and 28 are canceled herein without prejudice or disclaimer in order to advance prosecution of the present application and are under examination in continuation Application No. 11/924,707. Claims 18 and 25 are amended herein for clarity to more particularly define the invention. Support for the amendment of claims 18 and 25 to recite "wherein the nucleic acid is from a sample from a subject in need of warfarin therapy" is found in the language of claims 22 and 29, which are also canceled herein without prejudice. Support for the amendment of claims 18 and 25 to recite "a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:8" found throughout the specification, as set forth below. It is believed that no new matter is added by these amendments and their entry and consideration are respectfully requested. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Recordation of Interview Summary

To record the Interview Summary mailed on September 14, 2009 regarding the above-referenced patent application, applicants concur that the Interview Summary accurately reflects the substance of the telephone interview that took place on September 8, 2009, in which Examiner Jehanne S. Sitton and applicant's representative, Dr. Mary Miller, participated.

II. Support for amendments to claims 18 and 25

As discussed during the September 8, 2009 telephone interview, the specification provides the following written support for the amendment to claims 18 and 25 to recite "a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:8."

On page 19, lines 1-4:

> "Further provided herein are nucleic acids encoding VKOR and comprising one or more SNPs as described herein. Thus, the present invention further provides nucleic acids *comprising*,

> consisting essentially of and/or consisting of the nucleotide sequence as set forth in SEQ ID NOs:12, 13, 14, 15 and 16." (Emphasis added).

As shown in the Sequence Listing, the nucleotide sequences of SEQ ID NOs:12, 13, 14, 15 and 16 are all 5915 nucleotides in length and all match the nucleotide sequence of SEQ ID NO:11, which encompasses (i.e., comprises) the nucleotide sequence of SEQ ID NO:8, as set forth on page 14, lines 26-33:

> An example of a SNP correlated with an increased sensitivity to warfarin is a G→C alteration at nucleotide 2581 (SEQ ID NO:12) (in intron 2 of the VKOR gene; GenBank accession no. refSNP ID: rs8050894, incorporated by reference herein) of *the nucleotide sequence of SEQ ID NO:11, which is a reference sequence encompassing the genomic sequence of SEQ ID NO:8 and approximately 1000 nucleotides preceding and following this sequence. This sequence can be located as having the genome position "human chromosome 16p11.2" or in the physical map in the NCBI database as human chromosome 16: 31009700-31013800.* (Emphasis added).

Additional support for a VKOR genomic nucleotide sequence comprising the nucleotide sequence of SEQ ID NO:8 is found in the specification on page 3, lines 24-26 ("A further aspect of the present invention is an isolated nucleic acid encoding vitamin K epoxide reductase (VKOR), particularly mammalian (*e.g.*, human, ovine, bovine, monkey, etc.) VKOR."); on page 6, lines 19-21 ("As used herein, "nucleic acids" encompass both RNA and DNA, including cDNA, *genomic DNA*, synthetic (e.g., chemically synthesized) DNA and chimeras of RNA and DNA." (Emphasis added); on page 6, lines 30-32 ("Thus, in one embodiment, an isolated nucleic acid *includes some or all of the 5' non-coding (e.g., promoter) sequences* that are immediately contiguous to the coding sequence." (Emphasis added)); on page 16, line 31 through page 17, line 3 ("The *nucleotide sequence of the VKOR gene of a subject* is determined according to methods standard in the art, and as described in the Examples provided herein. For example, *genomic DNA* is extracted from cells of a subject and the *VKOR gene* is located and sequenced according to known protocols. Single nucleotide polymorphisms in the *VKOR gene* are identified by a comparison of a subject's sequence with the wild type sequence as known in the art (e.g., the reference sequence as shown herein as SEQ ID NO:11)" (Emphasis added)); and on page 24, lines 14-27 ("The search for the *VKOR gene* was focused on human chromosome sixteen between markers D16S3131 and D16S419. This region corresponds to chromosome 16 at

50cM-65cM on the genetic map and 26-46.3Mb on the physical map. 190 predicted coding sequences in this region were analyzed by a BLASTX search of the NCBI non-redundant protein database. Those human genes and orthologs from related species with known function were eliminated. Because VKOR appears to be a transmembrane protein (Carlisle & Suttie (1980) "Vitamin K dependent carboxylase: subcellular location of the carboxylase and enzymes involved in vitamin K metabolism in rat liver" *Biochemistry* 19:1161-7), the remaining genes were translated according to the cDNA sequences in the NCBI database and analyzed with the programs TMHMM and TMAP (Biology WorkBench, San Diego Supercomputer System) to predict those with transmembrane domains. *Thirteen genes* predicted to code for integral membrane proteins were chosen for further analysis." (Emphasis added)).

As also discussed with Examiner Sitton, further support for this amendment to claims 18 and 25, directed to embodiments of this invention describing amplification and oligonucleotide primers, is found throughout the specification, at least, for example, on page 4, lines 29-30 ("A further aspect of the present invention is an oligonucleotide that hybridizes to an isolated nucleic acid encoding VKOR as described herein."); page 7, lines 11-14 ("The term "oligonucleotide" refers to a nucleic acid sequence of at least about six nucleotides to about 100 nucleotides, for example, about 15 to 30 nucleotides, or about 20 to 25 nucleotides, which can be used, for example, as a primer in a PCR amplification or as a probe in a hybridization assay or in a microarray."); page 10, lines 24-25 and lines 32-34 ("The present invention further provides fragments and oligonucleotides of the nucleic acids of this invention , which can be used as primers and probes...Such fragments and oligonucleotides can be detectably labeled or modified, for example, to include and/or incorporate a restriction enzyme cleavage site when employed as a primer in an amplification (e.g., PCR) assay."); and on page 13, lines 5-12 ("The present invention further provides a method of detecting a nucleic acid encoding a VKOR polypeptide in a sample, comprising contacting the sample with a nucleic acid of this invention that encodes VKOR or a fragment thereof, or a complement of a nucleic acid that encodes VKOR or a fragment thereof, under conditions whereby a hybridization complex can form, and detecting formation of a hybridization complex, thereby detecting a nucleic acid encoding a VKOR polypeptide in a sample. Such hybridization assays are well known in the art and include probe detection assays and nucleic acid amplification assays.")

In addition, on page 20, lines 5-12, of the specification, "primers used to amplify the VKOR gene" are described. Among these is a primer having the nucleotide sequence of SEQ ID NO:29. This primer is located at nucleotides 935-953 of SEQ ID NO:11, which are outside of the nucleotide sequence of SEQ ID NO:8, which is comprised in the nucleotide sequence of SEQ ID NO:11 from nucleotide 1001 through nucleotide 4915. Furthermore, on page 21, lines 4-9, the identification of a SNP in the 5' UTR of the VKOR gene by "direct genomic DNA sequencing and SNP real-time PCR detection" is described. This SNP in the 5'UTR was designated vk563 (page 21, line 7 and Table 1) and is provided in the genomic nucleotide sequence of SEQ ID NO:15. (As previously explained to the Examiner and as set forth on page 19, lines 1-4, the nucleotide sequence of each of SEQ ID NOs:12-16 is the nucleotide sequence of SEQ ID NO:11 showing an allele of the SNPs exemplified in this invention.) This particular SNP site, vk563, is located at nucleotide 563 of SEQ ID NO:11, which is outside of the nucleotide sequence of SEQ ID NO:8, which as pointed out above, is comprised in the nucleotide sequence of SEQ ID NO:11 starting at nucleotide 1001. Thus, applicants believe that claims 18 and 25 as presented herein are adequately supported in the specification.

Having addressed all of the issues raised in the present Office Action and as discussed with Examiner Sitton, the applicants respectfully submit that all of the claims of this application are in condition for allowance, which action is respectfully requested. The Examiner is encouraged to contact the undersigned directly if such contact will expedite the allowance of the pending claims to issue.

No fee is believed due with this response. However, the Commissioner is authorized to charge any deficiency associated with this filing or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on September 14, 2009.

Claire Wimberly